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EXAMINER

KENEDY, ANDREW A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/020,025

Applicant(s)

LUO, SHUN

Examiner

Andrew A. Kenedy

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Amendment of Claims 1-3, 6-7, 9-11, 14-17, 20-22 and 29, and addition of Claims 30-36 in the reply of 01 June 2004, is acknowledged. Claims 1-36 are currently pending. Applicant's submission of a new declaration on 01 June 2004, which complies with CFR 1.67(a), is acknowledged.

The following rejections and/or objections are either reiterated or newly applied, and constitute the complete set presently being applied to Claims 1-36. The text of those sections of Title 35 U.S.C. not included in this action can be found in the previous Office Action.

Claim Rejections - 35 USC § 112

New Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While Applicant discloses the use of "laboratory automation systems such as...liquid handlers" for depositing samples into microtiter plates (see page 20, paragraph 1 of the instant specification), Applicant does not disclose a system that includes the use of a fluid-handling device to deposit reagents in array patterns in wells of microtiter plates. Furthermore, the phrase "fluid-handling device" does not appear in Applicant's claims or specification as originally filed, and Applicant has not pointed to any basis in the specification for the above limitations. Therefore, the above limitations of Claim 33 are deemed to constitute ***new matter*** that was not previously disclosed in Applicant's claims or specification as originally filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Rava et al. (US 5874219 A).

Regarding Claim 29, Rava et al. teaches a method and system for multiple parallel analysis of biological samples simultaneously (see at least col. 1, line 60 - col. 2, line 17; and Fig. 4), comprising: depositing an array of known reagents into as many wells of a glass bottom multi-well microtiter plate platform as desired for a particular assay and immobilizing each said array to said glass bottom thereof (see col. 2, lines 34-42; col. 9, lines 15-18; col. 4, lines 9-11; col. 8, lines 48-53; and col. 9, lines 36-60); depositing at least one labeled cDNA sample into at least one well of said multi-well microtiter plate platform (see at least col. 2, lines 12-17; and col. 3, line 44 – col. 4, line 5); depositing at least one said labeled cDNA sample into as many wells having a said array therein as desired for a particular assay (see at least col. 2, lines 43-48); allowing said each said labeled cDNA sample to hybridize to said array of known reagents in each said well (see at least col. 1, lines 34-41); reading said microtiter plate platform after hybridization is completed (see at least col. 2, lines 3-11); and using software, processing signals generated and read from said at least one label into a format useful for analysis (see at least col. 7, lines 10-19).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al. (US 6344316 B1) in view of Rava et al. (US 5874219 A).

Regarding Claims 1, 9 and 15, Lockhart et al. teaches a method and system of analyzing biological samples by probe arrays, comprising: obtaining a number of samples to be analyzed (see at least col. 22, lines 10-22); extracting RNA from each said sample to be analyzed (see at least col. 22, lines 10-22); isolating mRNA from said RNA to use as a template for synthesizing DNA (see at least col. 22, lines 23-30; and col. 23, lines 2-3); synthesizing cDNA from each said mRNA of each said sample (see at least col. 21, lines 27-50); labeling each said cDNA with a label (see at least col. 24, lines 54-67); labeling each said cDNA with one of either a first or a second label (see at least col. 24, lines 54-67); and using software, processing signals generated and read from said at least one label into a format useful for analysis (see at least col. 61, lines 15-23).

Regarding Claims 3, 11 and 17, Lockhart et al. teaches that the biological samples can be DNA, RNA, genes, DNA amplified from genes (portions of genes), nucleic acids (polynucleotides), nucleic acids derived from an mRNA (fragments of RNA), and DNA amplified from cDNA (fragments of DNA) (see at least col. 21, lines 45-50).

Art Unit: 1631

Regarding Claims 4, 12 and 18, Lockhart et al. teaches that the label can be a fluorescent label, a radio label, a colorimetric label, or colored glass or plastic beads (a reflective label) (see at least col. 24, lines 37-55)

Regarding Claims 5 and 13, Lockhart et al. teaches that the reading is performed on a device capable of reading a signal chosen from the group consisting of: fluorescence, radioactivity, color intensity, and reflection changes (see at least col. 47, lines 6-46).

Regarding Claims 7 and 15, Lockhart et al. teaches that each of two biological samples can be labeled with a different label of the same type, and provides an example of one sample being labeled with a green fluorescent label and a different sample being labeled with a red fluorescent label (see at least col. 24, lines 59-67).

Regarding Claims 8 and 19, Lockhart et al. teaches that the reading is performed using a device capable of simultaneously reading two of the same type of signals, where the signal can be fluorescence (see at least col. 24, lines 54-67; and col. 47, lines 6-28).

Regarding Claim 14, Lockhart et al. teaches that each cDNA from each said biological sample is labeled with the same label (see at least col. 22, lines 10-14; col. 24, lines 57-58; and col. 25, lines 64-68).

Regarding Claims 20-22, Lockhart et al. teaches that a labeled control target nucleic acid mixture (a control sample) can be used as an intra-array and inter-array normalization tool for assessing array variation by measuring variation in hybridization intensity of one or more labeled control target genes in the mixture (see at least col. 17, line 61 – col. 18, line 37; and col. 6, lines 11-19). That the control target sample can be labeled with the same or a different label from the experimental labeled cDNA sample is rendered obvious by the teachings above regarding Claims 1, 7, 8, 9, 14, 15, and 19, since the control sample contains

Art Unit: 1631

DNA just as the experimental sample and is therefore not subject to labeling requirements or limitations that are any different from experimental samples. Lockhart et al. teaches the use of labeled immobilized DNA probes to define background and align image for reading (see at least col. 31, line 48 – col. 33, line 27; col. 45, lines 37-41; and col. 57, lines 7-32) so that it would be within the ability of one of ordinary skill in the art to recognize that the labeled control samples used for normalizing variability of arrays could also be used for defining background and aligning the image for reading.

Regarding Claims 30-32, Lockhart et al. teaches that the reagents can be different species of oligonucleotides including deoxyribonucleotides (DNA) or ribonucleotides (RNA) in either single- or double-stranded form as well as known analogs of natural nucleotides (reagents chosen from the group of: DNA, RNA, PNA, genes, portions of genes, polynucleotides, fragments of DNA, fragments of RNA, short oligonucleotides) (see col. 6, lines 1-45).

Lockhart et al. does not teach the above limitations in the context of multi-well microtiter plate platform. However, Rava et al. teaches the assay of biological arrays in a multi-well microtiter plate platform format.

As in Applicant's Claims 1, 9, 15 and 20-22, Rava et al. teaches a method and system for multiple parallel and simultaneous analysis of samples, comprising: depositing an array of known reagents into as many wells of a multi-well microtiter plate platform as desired for a particular assay and immobilizing each said array thereon (see at least claims 1-5; col. 1, lines 60-67; col. 3, line 44; col. 7, line 64 - col. 8, line 8; and Fig. 4); depositing one, or more than one, labeled cDNA into at least one well of said multi-well microtiter plate platform (see at least claims 1-5; col. 10, line 66 - col. 11, line 14; col. 3, line 54-65); depositing at least one

Art Unit: 1631

said labeled cDNA into as many said wells having a said array therein as desired for a particular assay (see at least claims 1-5; and col. 2, lines 43-48); allowing each labeled cDNA to hybridize to said array of known reagents in each said well (see at least claims 1-5); and reading said microtiter plate platform after hybridization is completed (see at least claim 1; and col. 2, lines 26-30)

As in Applicant's Claims 2, 10 and 16, Rava et al. teaches that the number of biological samples to be assayed simultaneously is at least about 6 (see at least col. 4, lines 33-40; col. 7, line 65 – col. 8, line 8; and col. 9, lines 1-12)

As in Applicant's Claim 6, Rava et al. teaches that two biological samples are deposited in each well of said microtiter plate platform (see at least col. 9, lines 11-12; col. 9, lines 1-8; and col. 2, lines 47-48)

As in Applicant's Claim 23-25, Rava et al. teaches that the array of known reagents is deposited on the inner bottom surface of said well on an area in the maximum range of about 2.25mm x 2.25mm to about 36.0mm x 36.0mm, said area being dependent upon the number and size of wells formed in said microtiter plate platform and the density of the array deposited therein (col. 9, lines 28-30)

As in Applicant's Claim 26-28, Rava et al. teaches that the inner bottom surface of each said well is glass (col. 9, lines 36-44 and 52-57).

It would have been obvious for one of ordinary skill in the art to combine the teachings of Rava et al. regarding biological chip array technology in a multi-well microtiter plate platform, with the biological array methods and systems taught by Lockhart et al., since Rava et al. teaches: "This invention provides automated methods for concurrently processing multiple biological chip assays. Currently available methods utilize each biological chip

Art Unit: 1631

assay individually. The methods of this invention allow many tests to be set up and processed together. Because they allow much higher throughput of test samples, these methods greatly improve the efficiency of performing assays on biological chips" (col. 4, lines 33-40).

Response to Arguments

Applicant's arguments in the reply of 01 June 2004, have been fully considered.

Applicant's arguments were found by the Examiner either to be not persuasive, or to be moot as a result of Applicant's amendment of the claims.

Applicant argues at length regarding the Examiner's 112 1st Paragraph rejection of Claims 1-2, 4-10, 12-16 and 18-28 for failing to enable all types of "samples". Specifically, Applicant argues that the limitation of "samples" is enabled when viewed in the context of the invention as disclosed in the specification, and that one of ordinary skill in the art would recognize what constitutes a relevant sample for the purpose of executing Applicant's method. However, the Examiner notes that Applicant does not disclose a specific definition for the term "samples" in the instant specification. In the absence of a specific definition and without an inappropriate reading of limitations into the claims from the specification, the term "samples" is given its broadest reasonable interpretation. As such, the Examiner maintains that "samples" as claimed could reasonably include inorganic substances, for which Applicant's invention is not enabled. However, Applicant's arguments regarding the enablement of the method for "samples" is moot since Applicant has amended all of the relevant claims to recite "biological samples", which are inherently obtained from organisms, whether directly or indirectly, and routinely contain organic material. Consequently, the 112

Art Unit: 1631

1st Paragraph rejection is hereby withdrawn with respect to enablement of samples by the method.

Due to Applicant's amendment of the claims, the Examiner withdraws the 112 2nd Paragraph rejection of Claims 1-14, 20-21, 23-24, 26-27 and 29 for being drawn to a method and system without including limitations to a system in the body of the claims.

Due to Applicant's amendment of the claims, the Examiner withdraws the 112 2nd Paragraph rejection of Claim 29 for being unclear with respect to which component(s) mentioned in the claim actually constitute(s) the "samples".

Regarding the rejection of Claim 29 under 35 USC § 102(b), Applicant argues that Rava et al. does not teach microtiter plates with glass bottoms, or the depositing of arrays directly onto the inner bottom glass surface of such glass-bottomed microtiter plates. The examiner does not find this argument to be persuasive since Rava et al. teaches the following: "The biological chip plates used in the methods of this invention include biological chips. The array of probe sequences can be fabricated on the biological chip" (see col. 9, lines 15-18), and defines a biological chip as "A substrate having a surface to which one or more arrays of probes is attached. The substrate can be, merely by way of example, silicon or glass" (see col. 4, lines 9-11). These statements can be reasonably interpreted to mean that biological chips can be considered as one type of biological chip plate onto which arrays can be directly deposited. Rava et al. further teaches that "In one embodiment, the plates have the general size and shape of standard-sized microtiter plates having 96 wells arranged in an 8x12 format" (see col. 8, lines 48-51). Rava et al. further explains regarding the biological chip plates of the invention that "The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed

Art Unit: 1631

regions on which the probes are located,...the substrate may be functionalized glass,...Surfaces on the solid substrate usually, though not always, are composed of the same material as the substrate. Thus the surface may be composed of any of a wide variety of materials, for example:...silica or silica-based materials,...,inorganic glasses" (see col. 9, lines 36-60). One of ordinary skill in the art would reasonably interpret these teachings by Rava et al. as being a one-piece all-glass plate having glass-bottomed wells arranged in the general size and shape of a standard microtiter plate in at least one embodiment. Consequently, the Examiner finds Applicant's arguments not persuasive and maintains the rejection.

Regarding the rejection of Claims 1-28 under 35 USC § 103(a): **First**, Applicant again asserts at great length that Rava et al. does not teach depositing arrays directly onto the glass bottom of a glass bottom multi-well microtiter plate assay platform. The Examiner refers Applicant to the immediately preceding paragraph containing citations from Rava et al. and explanations presented as the basis for again finding this argument to not be persuasive. The Examiner would also like to reiterate an exemplary teaching from Rava et al. regarding the preferred format for the array platform: "In one embodiment, the plates have the general size and shape of standard-sized microtiter plates having 96 wells arranged in an 8x12 format. One advantage of this format is that instrumentation already exists for handling and reading assays on microtiter plates." (see col. 8, lines 48-53). **Second**, Applicant argues that Rava et al. requires a two-piece biological chip plate configuration wherein the probe arrays are pre-deposited on a wafer substrate base before assembling the microwell body top piece to create the finished microwell chip plate, or alternatively, pre-depositing the probe arrays onto chips and then depositing the entire chips into the wells of microtiter plates. Rava et al. does disclose and claim such embodiments. However, as explained and cited by the Examiner

Art Unit: 1631

immediately above and in the preceding paragraph, Rava et al. also discloses one-piece biological chip plates composed entirely of glass, having multiple depressions (wells) for depositing separate probe arrays, and having the same overall size and configuration as that of a standard microtiter plate. Such one-piece glass microtiter plates would require depositing the arrays directly onto the glass-bottomed wells after construction of the plate, and not pre-deposition, since the plates are one-piece all-glass. Furthermore, Rava et al. states that " a biological chip plate comprising a plurality of wells is provided. Each test well defines a space for the introduction of a sample and contains a biological array. The array is formed on a surface of the substrate, with the probes exposed to the space." (see col. 1, lines 63-27).

Since Rava et al. teaches that a biological chip plate can have a microtiter plate configuration with well bottoms comprising a substrate that can be glass for attaching probe arrays (see previous explanations and citations above), a reasonable interpretation of the preceding statement is that a finished microtiter plate is provided initially, and then the biological array of probes is subsequently formed (deposited) onto the glass well bottoms. **Third**, Applicant asserts that neither Lockhart et al. nor Rava et al. teach using single label analysis of multiple samples, using a single control for each type of array or each label, performing control or dose curves, or using two controls if two samples with different labels are being processed in each well. In instances where these limitations appear in the Applicant's instant claims, the Examiner maintains that these limitations are taught by the prior art and has attempted to address Applicant's assertions by clearly delineating the rejections and clearly citing column and line numbers to distinctly point out the teachings of these limitations where they appear in the prior art references (see the previous sections of this Office Action containing the rejections). **Fourth**, Applicant argues that the previous Office Action failed to show any

Art Unit: 1631

motivation in Rava et al., or in any other prior art, to modify Rava et al. to include features taught in Lockhart. The Examiner refers Applicant's attention to the fact that it was never suggested that the teachings of Lockhart be used to modify those of Rava et al. Precisely the reverse, that the innovative features of Rava et al. were to be used to modify the invention of Lockhart, since Rava et al. teaches their innovation of a multi-well platform as significantly increasing efficiency over traditional formats for processing biological arrays (see the motivation for the 35 USC § 103(a) rejection in the previous Office Action, which is also reiterated in the 35 USC § 103(a) rejection above).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew A. Kenedy whose telephone number is (571)-272-0574. The examiner can normally be reached on Monday-Friday 9:00am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Art Unit: 1631

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A.A.K. August 6, 2004

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

8/6/04

AU 1631